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Letter to the editor

Mechanisms underlie the proconvulsant effects of sildenafil

Sildenafil is a selective phosphodiesterase type 5 (PDE5) inhibitor, was approved by the FDA in 1998 for the treatment of erectile dysfunction [1]. Inhibition of the cGMP degradation and prolongation of NO effects including relaxation of the smooth muscle and consequently increase in blood flow in the corpus cavernosum was identified as the main mechanism of action of sildenafil. Although the discovery of sildenafil revolutionized the treatment of erectile dysfunction, it has been shown that it elicits side effects such as headache, blurred vision, and seizure. Generalized tonic-clonic seizure is a rare but life-threatening adverse effect of sildenafil reported even in people without any history of seizure or epilepsy [2,3]. Interestingly, Calabro et al. for the first time reported a case of recurrent generalized tonic-clonic seizures induced by sildenafil in a healthy young man with normal neurological examinations including computerized tomography (CT) scan and electrocardiogram (ECG) [3]. Other findings also reported generalized tonic-clonic seizure following consuming other PDE5 inhibitors such as vardenafil and tadalafil in healthy subjects [4–6] indicating that this adverse reaction is a class effect [7]. It has been suggested that activating the NO-cGMP pathway is involved in PDE5 inhibitors-induced seizure [3,8].

Furthermore, the administration of sildenafil for treating erectile dysfunction in epileptic patients is accompanied by increases in the risk of seizure attacks [9]. In this context, several studies were done to investigate the mechanisms involved in the proconvulsant effect of sildenafil. It should be mentioned that controversy exists on proconvulsant properties of sildenafil as some studies have reported the anticonvulsant effect of sildenafil [10]. Nieoczym et al. have reported the anticonvulsant effect of sildenafil in several models such as electroshock-induced seizures [11], PTZ-induced clonic seizures [12], and 6-Hz psychomotor seizure model [13]. This group showed that sildenafil dose-dependently increased the threshold for electrically and chemically induced seizures. Furthermore, sildenafil was demonstrated to elevated the anticonvulsant activity of well-known anti-epileptic drugs such as carbamazepine, valproate and topiramate through pharmacodynamics interactions. Similarly, Tawfik et al. reported the anticonvulsant action of sildenafil in the PTZ-kindling model of epilepsy [14]. They reported that the neuroprotective effects of sildenafil are related to reducing nitrative/oxidative stress as well as modulation of angiogenesis [14]. It has been suggested that sildenafil may have both pro and anticonvulsant activity depends on the experimental model of epilepsy, animal species, and the dose of sildenafil [15]. In this letter, we tried to provide an unbiased update on mechanisms underpinning sildenafil proconvulsant properties according to different investigations that have been done in experimental models of seizure.

One of the first endeavors, for finding mechanisms underlying proconvulsant effect of sildenafil was done in 2006 [8]. In pentylenetetrazole (PTZ) and bicuculline model of seizure, Riazi et al. showed that administration of NOS substrate, L-Arginine, or NO donor sodium nitroprusside in mice exacerbated the proconvulsant effects of sildenafil while it completely blocked by either NOS inhibitor L-NAME or guanylyl cyclase inhibitor methylene blue. These findings suggested direct evidence in favor of a NO-cGMP mediated modulation of seizure threshold by sildenafil [8]. Furthermore, in another study, it has been shown that the administration of sub-effective doses of sildenafil and L-arginine blocked the anticonvulsant effect of diazepam completely, while a combination of sub-effective doses of diazepam and L-NAME, inhibited the proconvulsant effect of sildenafil in the PTZ kindling model of epilepsy [16]. The results of this study indicated reducing NO production is involved in the anticonvulsant effects of diazepam. In line with previous reports, very recently we observed that NO plays a role in the seizure-inducing effects of sildenafil [17]. Hippocampal nitrite level was significantly increased in sildenafil treated mice and subsequently after PTZ-induced seizure. Moreover, proconvulsant effects of sildenafil are blocked by the administration of aminoguanidine, a selective iNOS inhibitor [17]. In a pilocarpine-induced seizures model, de Carvalho et al. demonstrated that sildenafil considerably increased iNOS and nNOS expression in the mice hippocampus [18]. In addition, they showed sildenafil dose and time-dependently exacerbated the NO production induced by pilocarpine [18]. Likewise, Rundfeldt et al. reported that NO inhibitors including NG-nitro-l-arginine and NG-nitro-l-arginine methyl ester increased the seizure threshold in rats [19].

The role of the opioid receptor also has been explored in proconvulsant effect of sildenafil [20]. In a PTZ model of seizure, Montaser-Kouhsari et al. showed that high doses of morphine, an opioid agonist, increased susceptibility to sildenafil seizure in mice while naltrexone inhibited the proconvulsant effect of sildenafil [20]. Previous studies suggested that opioid receptors could affect NO production [21], which is involved in proconvulsant effect of sildenafil, as mentioned earlier.

The downstream signaling of sildenafil also was investigated. It was shown sildenafil can increase the release of oxytocin (OXT) from the posterior pituitary [22] and subsequently, OXT could induce the phosphorylation of cyclic AMP response element-binding protein (CREB) and causes neural plasticity in the hippocampus [23]. Increased CREB phosphorylation in seizure has been found in both humans and rodents [24,25]. In another word, decreasing the CREB level has been suggested as a therapeutic strategy for the treatment of epilepsy [26]. CREB can enhance neuronal excitability in the hippocampus by changing the expression of its target genes including α1-$GABA_A$, BDNF, cyclooxygenase 2 (COX-2) and N-methyl D-aspartate receptor subtype 2B (NR2B) that are closely related to epilepsy [27]. Interestingly, it was shown that proconvulsant actions of sildenafil inhibited by the antagonism of OXT receptor whereas OXT administration potentiated it in PTZ-and Bicuculline-induced convulsion [23]. Furthermore, a recent study by our group showed that OXT had the same proconvulsant effects as sildenafil and both were blocked by the administration of cyclosporine A as a calcineurin inhibitor [17]. Calcineurin is a calcium/calmodulin regulated protein phosphatase that mediates the dephosphorylation of important

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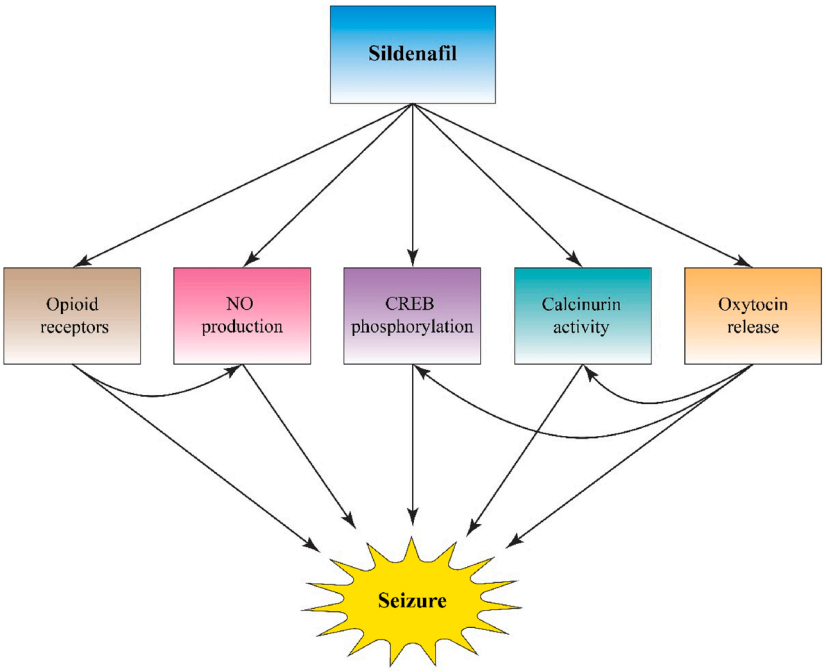

Fig. 1. A schematic representation of mechanisms involved in proconvulsant action of sildenafil.

synaptic receptors including NMDA and $GABA_A$ receptors [28,29]. Besides, inhibition of calcineurin activity has been shown anticonvulsant effects in various models of convulsion [30–32]. It has been suggested that the OXT receptor may activate the calcineurin/nuclear factor of activated T cells (NFAT) signaling and translocate NFAT to the nucleus through a calcineurin-mediated mechanism [33].

Although both convulsant and anti-convulsant actions have been reported following sildenafil administration, proconvulsant effects are more prominent in experimental and clinical investigations while limited findings are supporting the anticonvulsant effect of sildenafil. Regarding the wide use of sildenafil in the treatment of erectile dysfunction, understanding the mechanism underlying its proconvulsant properties may provide a better therapeutic strategy for minimizing this serious side effect of sildenafil. Fig. 1. summarize different signaling pathways that are involved in convulsant actions of sildenafil.

Author's statement

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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